Burkitt's Lymphoma Revisited: Series of Three Cases with Varied Clinical Presentation

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Abstract Burkitt's lymphoma is a form of non-Hodgkin's B-cell lymphoma with more than one identifiable variant. This tumour was first noted in Africans. The sporadic form most commonly presents with abdominal lymph node involvement. This tumour predominantly affects children and is probably the fastest growing tumours in humans, with exuberant proliferation. We here in report on three patients from our experience both adult and children who presented with varied clinical features.

Keywords Burkitt's lymphoma · c-myc · Non hodgkins lymphoma

Introduction

Burkitt's lymphoma is an infrequently occurring B cell lymphoma and is one of the most aggressive tumours known till date. There are three types of lymphoma; endemic, sporadic and HIV associated. The incidence of Burkitt's lymphoma is more in the tropics than in temperate countries and has a definite association with infections especially Epstein-Barr virus (EBV) and malaria [1]. They are recognized as small non-cleaved cell lymphomas displaying a starry sky

pattern due to the high rate of proliferation and spontaneous cell death. Chromosomal translocations involving the *MYC* oncogene are believed to highlight the hallmark of the disease. However the clinical presentation of Burkitt's lymphoma will differ depending upon the specific variant. In endemic areas, it usually involves the facial bones, particularly the jaw, maxilla, and orbit, especially in young children [2]. In comparison, the sporadic form tends to present in the lymphoid tissues of the gut, often presenting as masses in the Waldeyer ring or the terminal ileum, or even with massive abdominal involvement. Bone marrow involvement is commonly seen in progressive disease [3]. EBV involvement is reported in around 15–30 % of cases. The immunodeficient form is often associated with HIV infection, and may also be seen in post-transplant patients who are chronically immunosuppressed [4]. Generalized lymphadenopathy is usually noted in this variant. We report on three patients of Burkitt's lymphoma in different age groups and with varied clinical presentation from our tertiary care hospital who presented within a narrow span of last 45 days from Jul 2010 to Sep 2010 thus suggesting a possible seasonal association.

Patient 1

A 60 year old male presented with fever and generalised weakness of 1 month duration.

Clinical examination was unremarkable. Investigations revealed Hb-9.0 g/dL, Total leukocyte count 13,000/cmm, Plt-110,000/cmm, LDH-1785 U/L, HIV status was negative. USG abdomen revealed a retroperitoneal mass. Computed tomography (CT) guided Fine needle aspiration cytology (FNAC) of the retroperitoneal mass was suggestive of a lymphoproliferative disorder. Bone marrow aspirate revealed 80 % lymphoblast characterized by large

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Fig. 1 **A** Trucut biopsy of retroperitoneal mass (H&E 40×): There is diffuse infiltrate of atypical cells with numerous mitosis and a prominent starry sky pattern because of presence of tingible body macrophages (**B–D**): On IHC the neoplastic cells are CD 20 positive, Ki67-100 % positive and Tdt negative

cells with round to cleaved nucleus, indistinct nucleoli and moderate basophilic vacuolated cytoplasm. Occasional hand mirror cells were noted. Bone marrow biopsy was hypercellular and showed complete replacement by sheets of lymphoblasts. Tru-cut biopsy of retroperitoneal mass revealed Non-Hodgkin's lymphoma high grade. Immunohistochemistry (IHC) testing was positive for Ki-67 (100 %), CD20, CD10 and negative for TdT, CD3 (Fig. 1). IVAC regime (vincristine, doxorubicin, cyclophosphamide, cytarabine, methotrexate and folinic acid) was started however the patient expired on the 2nd day of chemotherapy.

Patient 2

A 4 years old male child presented with low grade fever, loss of appetite, weight loss of 8 months duration with GI bleed and loss of vision of 10 days duration. On physical examination, there was loss of vision in right eye. No peripheral lymphadenopathy was detected. Investigations revealed Hb-8.5 g/dL, Total leukocyte count 40,000/cmm, Platelets-80,000/cmm, PBS revealed 80 % lymphoblasts of FAB-ALL L3 morphology. Serum LDH was 2034 U/L and his HIV status was negative.

CECT abdomen showed circumscribed bowel thickening suggestive of small bowel mass measuring 10 × 08 cm, bilateral hydronephrosis, a mass lesion of dorsal vertebrae DV9-DV12 with enlarged mesenteric and retroperitoneal lymph nodes. Magnetic resonance imaging

Fig. 2 Routine cytology of CSF from spinal tap showing atypical lymphoid cells with cytoplasmic vacuolations

(MRI) Brain was suggestive of an extra-conal mass abutting the orbit. Cerebrospinal fluid cytology revealed numerous lymphoblasts of Burkitt's type (Fig. 2). PBS, Bone marrow aspirate and biopsy revealed Burkitt's lymphoma-leukemia syndrome. CT guided mesenteric lymph node biopsy revealed effacement of lymph node architecture by sheets of medium sized round cells with clumped chromatin and prominent nucleoli with increased mitosis and numerous macrophages giving a starry-sky pattern.

Immunohistochemistry performed on Lymph node biopsy was positive for Ki-67 (100 %), CD20, Latent membrane protein (LMP-1) and negative for CD3, TdT.

Patient 3

A 2years old male child presented with a history of left abdominal pain and lump with fever of one month duration. Physical examination was inconclusive. Investigations revealed Hb-9.5 g/dL, Total leukocyte count 13,000/cmm, Platelets-300,000/cmm, Serum LDH-1882 U/L, HIV status was negative. Peripheral blood examination done showed no atypical cells. USG-abdomen revealed left peritoneal swelling along with multiple hypo-echoic lesions in liver. Ultra sound guided FNAC of the mass lesion abdomen revealed features of lymphoproliferative disorder and the subsequent liver biopsy along with IHC was diagnostic of Burkitt's lymphoma.

Discussion

After the initial discovery of Burkitt's lymphoma by Denis Burkitt in 1958 the diagnosis of this aggressive lymphoma increased and it was found to be present throughout the tropics with a lesser predilection for areas with high altitude and colder regions.

Burkitt's lymphoma is a B Cell Lymphoma characterized by medium sized monomorphic cells usually having a MYC genetic dysregulation.

There are three types described each manifesting differently, having a separate pathogenesis and morphology. *Endemic* Burkitt's classically seen in Africa occurs in those patients infected with chronic malaria, *Sporadic* usually occurring due to genetic mutations, and *HIV associated* seen in immunocompromised patients [4].

Most cases of Burkitt's lymphoma are associated with EBV infection which has been proposed to be involved in the genetic dysregulation responsible for the development of Burkitt's lymphoma other than chronic immune stimulation [5]. Two cases described by us had EBV infection as seen by LMP-1 stain on IHC.

Another potential precipitant of Burkitt's lymphoma is malaria as seen in the endemic variant, and there are various unknown environmental factors yet to be described involved in the pathogenesis, however all these converge in a common pathogenic mechanism involving the MYC gene [6].

The ileocecal area is the most common site involved [7]. Lymph node involvement is more common among adults than among children. Kidneys, gastrointestinal tract, ovaries, breast, and other extranodal sites are also involved. Patients may also have malignant pleural effusions or ascites [8]. Neoplastic cells are EBV+ in 15–30 % of cases, or fewer in some series [9]. Burkitt's lymphoma accounts for 30–40 % of non-Hodgkin's lymphoma in HIV+ patients [10].

With respect to morphology, the WHO classification describes classic Burkitt's lymphoma and two variants Burkitt's lymphoma with plasmacytoid differentiation and atypical Burkitt's/Burkitt-like lymphoma.

Classic Burkitt's lymphoma is usually seen in endemic variants and few sporadic cases whereas those with immune deficiency usually have plasmacytoid differentiation. Burkitt-like lymphoma and Burkitt's lymphoma with plasmacytoid differentiation both tend to have greater nuclear pleomorphism than classic Burkitt's lymphoma, and both tend to have a smaller number of more prominent nucleoli. The plasmacytoid variant has, in addition, monotypic cytoplasmic immunoglobulin. Burkitt's lymphoma, regardless of subtype, typically expresses monotypic surface IgM, pan-B-cell antigens, including CD19, CD20, CD22, and CD79a, and coexpresses CD10, Bcl-6, CD43, and p53, but not CD5, CD23, Bcl-2, CD138, or TdT [11].

A defining feature of Burkitt's lymphoma is the presence of a translocation between the *c-myc* gene and the *IgH* gene (found in 80 % of cases [t(8;14)] or between *c-myc* and the gene for either the kappa or lambda light chain (*IgL*) in the remaining 20 % [t(2;8) or t(8;22)], respectively [12].

The differential diagnosis of Burkitt's lymphoma are other types of high-grade B-cell lymphomas, especially diffuse large B-cell lymphoma. Features that favor Burkitt's lymphoma include morphology, an immunophenotype that is CD20+, CD10+, Bcl-6+, Bcl-2–, TdT–, and monotypic sIg+, with virtually all cells Ki67 (proliferation) positive, and a translocation involving *c-myc* and *IgH* or *IgL*, without rearrangements involving the *bcl-2* or *bcl-6* genes.

c-Myc protein expression has been suggested to favour Burkitt's lymphoma over diffuse large B-cell lymphoma.

Other entities in the differential diagnosis of Burkitt's lymphoma include lymphoblastic lymphoma/leukemia and blastoid mantle cell lymphoma.

Staging is performed using the Ann Arbor or, more often, the St Jude/Murphy staging system [13]. Approximately 30 % of patients present with limited-stage disease (I or II), while 70 % present with widespread disease (stage III or IV) [6]. Patients often present with bulky disease, frequently with an elevated lactate dehydrogenase (LDH) level. Patients with any of the three clinical variants are at risk for spread to the central nervous system (CNS) and bone marrow.

The bone marrow is positive in 30–38 %, and the CNS is involved in 13–17 % of adult cases. In our cases one had CNS involvement and all three had bone marrow infiltration.

Sporadic and immunodeficiency-associated Burkitt's lymphoma do not share endemic Burkitt's lymphoma's

exquisite sensitivity to chemotherapy, so the prognosis is poor, particularly among adults. Short-duration, high-intensity chemotherapy, yields excellent survival in children. Patients with localized disease have a >90 % 5-year survival rate [14], and children with widespread disease (including leukemic presentation) may achieve a >90 % complete response (CR) rate.

The institution of the CODOX-M/IVAC regimen (Magrath protocol)—two cycles of CODOX-M (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate, and intrathecal therapy) alternating with IVAC (ifosfamide, etoposide, high-dose cytarabine, and intrathecal therapy) represents a major step in the treatment of Burkitt's lymphoma [15].

Of our three patients two responded to chemotherapy are on close followup in haematology OPD.

Conclusion

Burkitt's lymphoma is an aggressive B cell lymphoma with several variants and has varied presentation. Early diagnosis is essential as it is highly proliferative malignancy. The role of the hematopathologist is supreme as it is only after the diagnosis that further treatment and prognostication be planned. An astute pathologist can clinch the diagnosis early with only the examination of the peripheral blood smear as demonstrated in our case series report.

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